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(54) Tetrahydronaphthalene and indane derivatives.

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GB-A- 1 394 859
US-A- 3 621 101
US-A- 4 505 932

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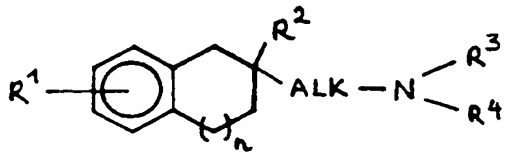
Description

The invention relates to tetrahydronaphthalene and indane derivatives with the general formula I:



I

wherein

R^1	represents zero to four substituents, which may be the same or different and are selected from OH, halogen, NO_2, CN, CF_3, C_1-C_4 alkyl C_1-C_4 alkoxy and unsubstituted or C_1-C_4 alkyl substituted amino;
R^2	represents C_1-C_4 alkyl, C_1-C_4 alkenyl and C_1-C_4 alkynyl which may be substituted by halogen;
R^3 and R^4	represent independently H, C_1-C_4 alkyl or form together with the nitrogen atom a 5- or 6-membered ring;
n	has the value 0 or 1;
ALK	is an aliphatic hydrocarbon with 1-8 carbon atoms;

and their pharmaceutically acceptable salts.

These new compounds are typical monoamine reuptake blockers with additional α_2 antagonist activity and show strong anti-depressant activity without being sedative. Compounds according to this invention are also suitable for treating patients with anxiety disorders, e.g. panic disorder.

Preferred compounds of formula I have an unsubstituted, mono- or disubstituted aromatic nucleus and a substituent R^2 being C_1-C_4 alkyl whereas R^3 and R^4 are selected from H, C_1-C_4 alkyl or together with the nitrogen atom form a piperazine or 4-methylpiperazine ring and ALK is methylene or ethylene.

Among those preferred compounds the most active compounds are tetrahydronaphthalene and especially indane derivatives, wherein the aromatic nucleus is unsubstituted and R^2 is CH_3, R^3 is CH_3 or H with a preference for H, R^4 is H and ALK is methylene.

The term C_1-C_4 alkyl, used in the definition of general formula I, means an alkyl group with 1 to 4 carbon atoms, viz. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl.

The term C_1-C_4 alkoxy means an alkoxy group in which the term alkyl has the similar meaning as above.

The terms C_1-C_4 alkenyl and C_1-C_4 alkynyl mean unsaturated hydrocarbons of 1 to 4 carbon atoms with double or triple bonds respectively. Examples are vinyl, allyl, isopropenyl, ethynyl, 1-butynyl, and the like.

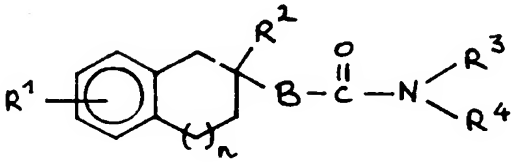
The term ALK means an aliphatic hydrocarbon with 1-8 carbon atoms, which may be branched or straight-chained. Preferably this hydrocarbon is a saturated hydrocarbon with 1-4 carbon atoms, such as the methylene, ethylene, propylene and butylene group.

The 5- and 6-membered ring, mentioned in the definition of R^3 and R^4 is a heterocyclic ring which may contain an additional hetero atom, such as pyrrolidine, piperidine, morpholine, piperazine, dihydro-imidazole, pyrazolidine, imidazolidine, this ring may be substituted with C_1-C_4 alkyl. Particularly useful are the piperazine and 4-methylpiperazine rings.

Pharmaceutical acceptable salts are acid addition salts derived from acids, such as hydrochloric acid, sulphuric acid, phosphoric acid, acetic acid, propionic acid, glycolic acid, maleic acid, fumaric acid, malonic acid, succinic acid, tartaric acid, lactic acid, citric acid, ascorbic acid, salicylic acid, benzoic acid, methanesulphonic acid, obtained by reaction of the free base according to formula I with an appropriate acid in a suitable solvent.

The compounds of this invention may be prepared by any method known for the preparation of analogous compounds.

A suitable method for the preparation of compounds I is reduction of an amide of general formula II:

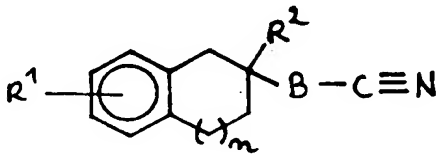


II

wherein R^1, R^2, R^3, R^4, and n have the aforesaid meanings, and B is a bond between the ring and the carbonyl group or is an aliphatic hydrocarbon with 1 to 7 carbon atoms.

Suitable reduction means are those commonly in use in the reduction of amides, e.g. metalhydrides, and preferably $LiAlH_4$, borane or a mixture of $LiAlH_4$ and $AlCl_3$ in a suitable solvent, like, tetrahydrofuran, diethylether, benzene and the like.

Compounds of general formula I, wherein R^3 and R^4 are H, can also be obtained by reduction of a carbonitrile with general formula III:

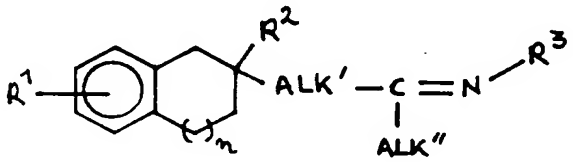


III

wherein R^1, R^2, n and B have the aforesaid meanings.

Reduction means and solvents commonly used in the reduction of nitriles may be employed.

Compounds of general formula I, wherein R^4 is H may be obtained by reduction of a Schiff base of general formula IV:



IV

wherein R^1, R^2 and n have the aforesaid meanings, R^3 is hydrogen or $C_1 - C_4$ alkyl and ALK' – C – ALK" has the same carbon atom skeleton as ALK, with a suitable reducing agent, e.g. sodium borohydride in methanol or ethanol.

Compounds according to formula I, in so far as R^3 and/or R^4 are H, may be converted into other compounds according to the invention. For example, reaction with formaldehyde and formic acid leads to compounds where R^3 and/or R^4 are CH_3. Reaction with alkylhalogenide leads to alkyl substitution at nitrogen, which can be performed advantageously through its trifluoroacetamide.

When compounds of the general formula I contain chiral atoms, the pure enantiomers as well as the mixtures thereof including the racemic mixture, belong to the invention.

The pure enantiomers can be obtained by stereoselective synthesis or by resolution of the racemic endproduct or precursors thereof.

Compounds according to this invention can be mixed with a suitable pharmaceutical carrier in order to obtain a pharmaceutical preparation for either oral, local or parenteral administration.

Preferred daily dose is between 0.01 and 50 and more preferably between 0.1 and 10 mg/kg body weight and for human use a daily dose between 5 and 500 mg is common. For the purpose of administration the compound of the invention is processed in the form suitable for oral, local or parenteral administration, for example as a tablet, pill capsule, solution, emulsion, paste or spray. The oral form is the most preferred form of administration.

The following examples further illustrate the preparation of the compounds used in this invention.

Example 1

1,2,3,4 – Tetrahydro – 2,N – dimethylinaphthalene – 2 – methanamine (Z) – 2 – butenedioate (1:1)

A solution of 1,2,3,4 – tetrahydro – 2,N – dimethylnaphthalene – 2 – carboxamide (10 g) in tetrahydrofuran (90 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (2.5 g) in tetrahydrofuran (10 ml) at such a rate that a gentle reflux was maintained. After the addition had been completed, the reaction mixture was refluxed for a further half hour then it was cooled and excess reagent was destroyed by careful addition of water.

The resulting mixture was filtered, and evaporation of the filtrate gave the amine as an oil. This was converted to the maleate salt in the usual manner and recrystallised from methanol/ether to give pure 1,2,3,4 – tetrahydro – 2,N – dimethylnaphthalene – 2 – methanamine (Z) – 2 – butenedioate (1:1), mp 132 – 135 °C.

Example 2

In an analogous manner as described in example 1 was prepared:
1,2,3,4 – Tetrahydro – 2 – methylnaphthalene – 2 – methanamine hydrochloride, mp 211 – 212 °C;
1,2,3,4 – Tetrahydro – 2,N, N – trimethylnaphthalene – 2 – methanamine hydrochloride, mp 184 – 195 °C;
2 – Ethyl – 1,2,3,4 – tetrahydronaphthalene – 2 – methanamine hydrochloride, mp 151 °C;
2 – Ethyl – 1,2,3,4 – tetrahydro – N – methylnaphthalene – 2 – methanamine hydrochloride, mp 203 °C;
1,2,3,4 – Tetrahydro – 2,N – dimethylnaphthalene – 2 – ethanamine hydrochloride, mp 201 °C;
1,2,3,4 – Tetrahydro – 2 – (3 – propenyl) – naphthalene – 2 – methanamine hydrochloride, mp 159 °C;
1,2,3,4 – Tetrahydro – N – methyl – 2 – (3 – propenyl) – naphthalene – 2 – methanamine hydrochloride, mp 197 °C;
6 – Chloro – 1,2,3,4 – tetrahydro – 2,N – dimethylnaphthalene – 2 – methanamine hydrochloride, mp 255 °C;
6 – Chloro – 1,2,3,4 – tetrahydro – 2 – methylnaphthalene – 2 – methanamine hydrochloride, mp 193 °C;
7 – Chloro – 1,2,3,4 – tetrahydro – 2 – methylnaphthalene – 2 – methanamine hydrochloride, mp 210 °C;
7 – Chloro – 1,2,3,4 – tetrahydro – 2,N – dimethylnaphthalene – 2 – methanamine hydrochloride. mp 213 °C;
1,2,3,4 – Tetrahydro – 6 – methoxy – 2,N – dimethylnaphthalene – 2 – methanamine hydrochloride, mp 215 °C;
1,2,3,4 – Tetrahydro – 7 – methoxy – 2,N – dimethylnaphthalene – 2 – methanamine hydrochloride, mp 193 °C;
2 – Ethynyl – 1,2,3,4 – tetrahydro – N – methylnaphthalene – 2 – methanamine (Z) – 2 – butenedioate (1:1), mp 142 °C dec.;
2 – Fluoromethyl – 1,2,3,4 – tetrahydro – N – methylnaphthalene – 2 – methanamine hydrochloride, mp 169 °C;
2,3 – Dihydro – 2,N – dimethyl – 1H – indene – 2 – methanamine hydrochloride, mp 218 °C;
5 – Chloro – 2,3 – dihydro – 2,N – dimethyl – 1H – indene – 2 – methanamine hydrochloride, mp 206 °C;
5,6 – Dichloro – 2,3 – dihydro – 2,N – dimethyl – 1H – indene – 2 – methanamine hydrochloride, mp 244 °C;
2,3 – Dihydro – 2,N – dimethyl – 1H – indene – 2 – ethanamine hydrochloride, mp 178 °C;
5,6 – Dichloro – 2,3 – dihydro – 2,N – dimethyl – 1H – indene – 2 – ethanamine hydrochloride, mp 229 °C;
1 – (2,3 – Dihydro – 2 – methyl – 1H – 2 – indenylmethyl)piperazine dihydrochloride, mp 267 °C (dec).
1 – (5,6 – Dichloro – 2,3 – dihydro – 2 – methyl – 1H – 2 – indenylmethyl)piperazine dihydrochloride, mp 275 °C (dec);
1 – Methyl – 4 – (1,2,3,4 – tetrahydro – 2 – methyl – 2 – naphthalenylmethyl) piperazine dihydrochloride, mp 253 °C;
1 – (1,2,3,4 – Tetrahydro – 2 – methyl – 2 – naphthalenylmethyl) piperazine dihydrochloride mp. 251 °C;

Example 3

1,2,3,4 – Tetrahydro – N – methyl – 2 – (1 – methylethyl) – naphthalene – 2 – methanamine hydrochloride.

A solution of borane – tetrahydrofuran complex in tetrahydrofuran (14 ml of 1M – 1.5 mole equiv.) was added to a solution of 1,2,3,4 – tetrahydro – N – methyl – 2 – (1 – methylethyl) – naphthalene – 2 – carboxamide (2.1 g) in tetrahydrofuran (5 ml). The resulting solution was left standing at room temperature for eleven days, then it was acidified with hydrochloride acid and refluxed for eight hours.

The reaction mixture was diluted with water and extracted with ether. The aqueous phase was then made strongly alkaline with ammonium hydroxide, and the product was extracted into ether.

Passage of gaseous hydrogen chloride gave a precipitate of the salt which was isolated by filtration and recrystallized from methanol/ether to give 1,2,3,4 – tetrahydro – N – methyl – 2 – (1 – methylethyl) – naphthalene – 2 – methanamine hydrochloride (1.2 g), mp 261 °C.

Example 4

1,2,3,4 – Tetrahydro – 2 – (1 – methylethyl) – naphthalene – 2 – methanamine (Z) – 2 – butenedioate (1:1)

A solution of 1,2,3,4 – tetrahydro – 2 – (1 – methylethyl)naphthalene – 2 – carbonitrile (3.5 g) in dry ether (35 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (1.5 g) in dry ether (15 ml). The reaction mixture was then refluxed for thirty minutes.

After excess reagent had been destroyed by careful addition of water, the mixture was filtered and the filtrate was evaporated to an oil (3.4 g). The crude amine was converted to the maleate salt and crystallized from methanol/ether to give:
1,2,3,4 – tetrahydro – 2 – (1 – methylethyl) – naphthalene – 2 – methanamine (Z) – 2 – butenedioate (1:1) (4 g), mp 109 °C.

Example 5

In an analogous manner as described in Example 4 was prepared:
2,3 – Dihydro – 2 – methyl – 1H – indene – 2 – methanamine hydrochloride, mp 228 °C;
5 – Chloro – 2,3 – dihydro – 2 – methyl – 1H – indene – 2 – methanamine hydrochloride, mp 217 °C;
1,2,3,4 – Tetrahydro – 2 – methylnaphthalene – 2 – ethanamine hydrochloride, mp 216 °C;
1,2,3,4 – Tetrahydro – 2 – methylnaphthalene – 2 – propanamine hydrochloride, mp 129 °C;

Example 6

N – Ethyl – 1,2,3,4 – tetrahydro – 2 – methylnaphthalene – 2 – methanamine hydrochloride.

Trifluoroacetic anhydride (14.2 ml) was added dropwise to a solution of 1,2,3,4 – tetrahydro – 2 – methylnaphthalene – 2 – methanamine (11.7 g) and triethylamine (10 ml) in dichloromethane (100 ml) at 10 – 15 °C. When the addition had been completed, water was added and the layers were separated. The organic layer was washed three times with water, then dried over sodium sulphate and evaporated to give the trifluoroacetamide (18 g), mp 73 °C.

Finally powdered potassium hydroxide (3.3 g) was added all at once to a solution of the trifluoroacetamide (4 g) in dry acetone (100 ml) and iodoethane (4.7 ml) just as it reached boiling point. The mixture was refluxed for half an hour, then the solvent and excess iodoethane were distilled off under reduced pressure. The residue was refluxed with 50% aqueous acetone (100 ml) for half an hour, then the mixture was extracted with ether and evaporated to give crude N – ethyl – 1,2,3,4 – tetrahydro – 2 – methylnaphthalene – 2 – methanamine (3 g). This material was purified by chromatography on silica gel eluted with dichloromethane containing an increasing proportion of methanol and ammonium hydroxide, and the purified amine was converted to the hydrochloride salt. Recrystallization from methanol/ether gave N – ethyl – 1,2,3,4 – tetrahydro – 2 – methylnaphthalene – 2 – methanamine hydrochloride (1.8 g), mp 180 °C.

Example 7

In an analogous manner as described in Example 6 was prepared:

1,2,3,4 – tetrahydro – N – methyl – 2 – (3 – propenyl) – naphthalene – 2 – methanamine hydrochloride, mp 197 °C;

Example 8

2 – Ethyl – 1,2,3,4 – tetrahydro – N,N – dimethylnaphthalene – 2 – methanamine hydrochloride.

A solution of 2 – ethyl – 1,2,3,4 – tetrahydro – N – methylnaphthalene – 2 – methanamine (3g) in formic acid (4.5 ml) and 40% aqueous formaldehyde (4.5 ml) was heated at 90 °C for six hours. The resulting solution was cooled, diluted with water, and basified with sodium hydroxide solution. The product was extracted with ether and the extract was dried over sodium sulphate. Passage of gaseous hydrogen chloride gave a precipitate of the salt which was collected and recrystallized from dichloromethane/ether to give 2 – ethyl – 1,2,3,4 – tetrahydro – N,N – dimethylnaphthalene – 2 – methanamine hydrochloride (1.2 g), mp 157 °C.

Example 9

In an analogous manner as described in Example 8 was prepared:
1,2,3,4 – Tetrahydro – N,N – dimethyl – 2 – (3 – propenyl)naphthalene – 2 – methanamine hydrochloride;
1,2,3,4 – Tetrahydro – N,N – dimethyl – 2 – (1 – methylethyl)naphthalene – 2 – methanamine hydrochloride, mp 195 °C.

Example 10

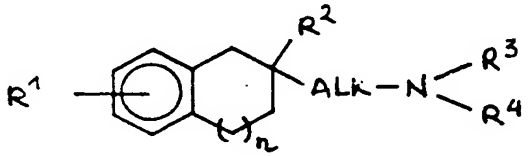
2,3 – Dihydro – 2,N,α – trimethyl – 1H – indene – 2 – methanamine hydrochloride

2 – Acetyl – 2,3 – dihydro – 2 – methyl – 1H – indene (3 g) was dissolved in a solution of methylamine in ethanol (15 ml; 33% w/w) and the solution was allowed to stand at room temperature for 16 h. Sodium borohydride (750 mg) was added to the solution and after 1 h the solution was evaporated to a small volume and water was added. The amine was isolated by extraction into ether and converted in the usual manner to the hydrochloride salt which was crystallized from methanol to give the titled compound (2 g), m.p. 254 °C.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, NL, SE

1. Tetrahydronaphthalene and indane derivatives of the general formula I:



I

wherein

R^1	represents zero to four substituents, which may be the same or different and are selected from OH, halogen, NO_2, CN, CF_3, $C_1 - C_4$ alkyl, $C_1 - C_4$ alkoxy and unsubstituted or $C_1 - C_4$ alkyl substituted amino;
R^2	represents $C_1 - C_4$ alkyl, $C_1 - C_4$ alkenyl and $C_1 - C_4$ alkynyl which may be substituted by halogen;
R^3 and R^4	represent independently H, $C_1 - C_4$ alkyl or form together with the nitrogen atoms a 5 – or 6 – membered ring;
n	has the value 0 or 1;
ALK	is an aliphatic hydrocarbon with 1 – 8 carbon atoms

and their pharmaceutically acceptable salts.

2. Compounds according to claim 1, with an unsubstituted, mono – or disubstituted aromatic nucleus wherein R^2 is $C_1 - C_4$ alkyl, R^3 and R^4 are selected from H, $C_1 - C_4$ alkyl or together with the nitrogen atom form a piperazine or 4 – methylpiperazine ring, ALK is methylene or ethylene, and their pharmaceutically acceptable salts.

3. Compounds according to claim 1 or 2, wherein the aromatic nucleus is unsubstituted and R^2 is CH_3, R^3 is CH_3 or H, R^4 is H, ALK is methylene, n is 0 or 1 and their pharmaceutically acceptable salts.

4. Compounds according to claims 1 – 3, wherein the aromatic nucleus is unsubstituted and R^2 and R^3 are CH_3, R^4 is H, ALK is methylene, n is 0 or 1, and their pharmaceutically acceptable salts.

5. Compounds according to claims 1 – 3, wherein the aromatic nucleus is unsubstituted and R^2 is CH_3, R^3 and R^4 are H, ALK is methylene, n is 0, and their pharmaceutically acceptable salts.

6. Process of analogy for the preparation of a compound according to claim 1, wherein an amide of formula II, a nitrile of formula III or a Schiff base of formula IV is reduced, after which the compound of formula I thus obtained (a) may be N – alkylated in so far as R^3 and/or R^4 are hydrogen and/or (b) may be converted into a pharmaceutically acceptable salt.

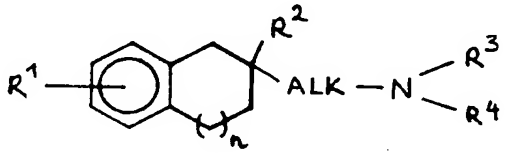
7. Pharmaceutical preparation containing a compound according to claim 1 as the active principle in admixture with a pharmaceutically acceptable carrier.

8. Use of compounds according to claim 1 for the preparation of a medicament with anti – depressant activity.

9. The compounds of any one of claims 1 – 5 for use in therapy.

Claims for the following Contracting States : ES, GR

1. A process for the preparation of tetrahydronaphthalene and indane derivatives having the general formula I:

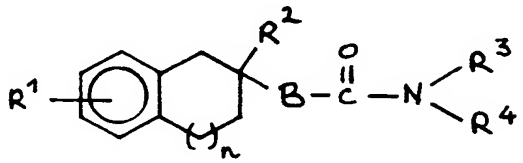


I

wherein

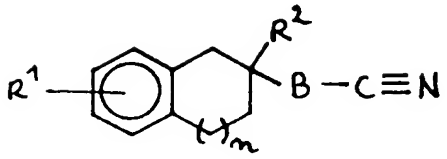
R^1	represents zero to four substituents, which may be the same or different and are selected from OH, halogen, NO_2, CN, CF_3, $C_1 - C_4$ alkyl, $C_1 - C_4$ alkoxy and unsubstituted or $C_1 - C_4$ alkyl substituted amino;
R^2	represents $C_1 - C_4$ alkyl, $C_1 - C_4$ alkenyl and $C_1 - C_4$ alkynyl which may be substituted by halogen;
R^3 and R^4	represent independently H, $C_1 - C_4$ alkyl or form together with the nitrogen atoms a 5 – or 6 – membered ring;
n	has the value 0 or 1;
ALK	is an aliphatic hydrocarbon with 1 – 8 carbon atoms,

and their pharmaceutically acceptable salts,
characterized in that an amide of formula II



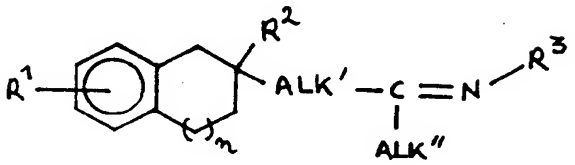
II

a nitrile of formula III



III

or a Schiff base of formula IV



IV

is reduced, after which the compound of formula I thus obtained (a) may be N-alkylated in so far as R^3 and/or R^4 are hydrogen and/or (b) may be converted into a pharmaceutically acceptable salt.

2. The process according to claim 1, wherein the aromatic nucleus is unsubstituted , mono- or disubstituted, and R^2 is C_1-C_4 alkyl, R^3 and R^4 are selected from H, C_1-C_4 alkyl or together with the nitrogen atom form a piperazine or 4-methylpiperazine ring and ALK is methylene or ethylene.

3. The process according to claim 1 or 2, wherein the aromatic nucleus is unsubstituted and R^2 is CH_3, R^3 is CH_3 or H, R^4 is H, ALK is methylene and n is 0 or 1.

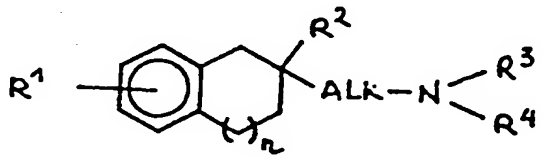
4. The process according to claims 1-3, wherein the aromatic nucleus is unsubstituted and R^2 and R^3 are CH_3, R^4 is H, ALK is methylene and n is 0 or 1.

5. The process according to claims 1-3, wherein the aromatic nucleus is unsubstituted and R^2 is CH_3, R^3 and R^4 are H, ALK is methylene and n is 0.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, NL, SE

1. Tetrahydronaphthalin- und Indanderivate der allgemeinen Formel I :



I

in welcher

R^1	null bis vier Substituenten bedeutet, welche gleich oder verschieden sein können und ausgewählt sind aus OH, Halogen, NO_2, CN, CF_3, C_1-C_4-Alkyl, C_1-C_4-Alkoxy und unsubstituiertem oder mit C_1-C_4-Alkyl substituiertem Amino;
R^2	C_1-C_4-Alkyl, C_1-C_4-Alkenyl und C_1-C_4-Alkynyl bedeutet, welches mit Halogen substituiert sein kann;
R^3 und R^4	unabhängig voneinander H, C_1-C_4-Alkyl bedeuten oder zusammen mit den Stickstoffatomen einen 5- oder 6-gliedrigen Ring bilden;
n	den Wert 0 oder 1 aufweist;
ALK	ist ein aliphatischer Kohlenwasserstoff mit 1-8 Kohlenstoffatomen,

und deren pharmazeutisch annehmbare Salze.

2. Verbindung nach Anspruch 1 mit einem unsubstituierten, mono- oder disubstituierten aromatischen Kern, in welchem R^2 C_1-C_4-Alkyl ist, R^3 und R^4 ausgewählt aus H, C_1-C_4-Alkyl oder zusammen mit dem Stickstoffatom einen Piperazin- oder 4-Methylpiperatzinring bilden, ALK Methylen oder Aethylen ist, und deren pharmazeutisch annehmbare Salze.

3. Verbindungen nach Anspruch 1 oder 2, in welchen der aromatische Kern unsubstituiert ist und R^2 CH_3 bedeutet, R^3 CH_3 oder H ist, R^4 H ist, ALK Methylen ist, n 0 oder 1 bedeutet, und deren pharmazeutisch annehmbare Salze.

4. Verbindungen nach den Ansprüchen 1-3, in welchen der aromatische Kern unsubstituiert ist und R^2 und R^3 CH_3 bedeuten, R^4 H ist, ALK Methylen ist, n 0 oder 1 bedeutet, und deren pharmazeutisch annehmbare Salze.

5. Verbindungen nach den Ansprüchen 1-3, in welchen der aromatische Kern unsubstituiert ist und R^2 CH_3 bedeutet, R^3 und R^4 gleich H sind, ALK Methylen ist, n gleich 0 ist, und deren pharmazeutisch annehmbare Salze.

6. Analogieverfahren für die Herstellung einer Verbindung nach Anspruch 1, dadurch gekennzeichnet, dass ein Amid der Formel II, ein Nitril der Formel III oder eine Schiff'sche Base der Formel IV reduziert wird, worauf die derart erhaltene Verbindung der Formel I (a) N-alkyliert werden kann, sofern R^3 und/oder R^4 Wasserstoff sind und/oder (b) in ein pharmazeutisch annehmbares Salz umgewandelt werden kann.

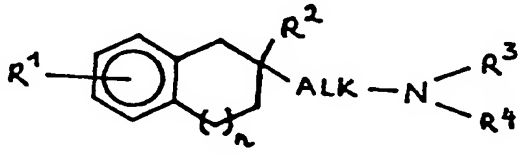
7. Pharmazeutisches Präparat, welches eine Verbindung nach Anspruch 1 als aktive Komponente vermischt mit einem pharmazeutisch annehmbaren Träger enthält.

8. Verwendung von Verbindungen nach Anspruch 1 für die Herstellung eines Arzneimittels mit antidepressanter Wirksamkeit.

9. Verbindungen nach einem der Ansprüche 1-5 zur Verwendung in der Therapie.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung von Tetrahydronaphthalin- und Indan-Derivaten der allgemeinen Formel I:

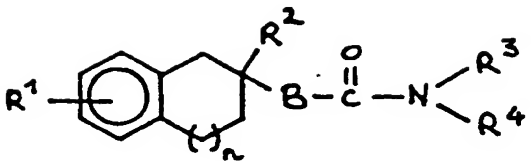


I

in welcher

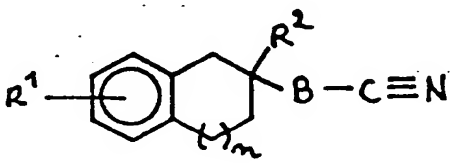
R^1	null bis vier Substituenten bedeutet, welche gleich oder verschieden sein können und ausgewählt sind aus OH, Halogen, NO_2, CN, CF_3, C_1-C_4-Alkyl, C_1-C_4-Alkoxy und unsubstituiertem oder mit C_1-C_4-Alkyl substituiertem Amino;
R^2	C_1-C_4-Alkyl, C_1-C_4-Alkenyl und C_1-C_4-Alkynyl bedeutet, welches mit Halogen substituiert sein kann;
R^3 und R^4	unabhängig voneinander H, C_1-C_4-Alkyl bedeuten oder zusammen mit den Stickstoffatomen einen 5- oder 6-gliedrigen Ring bilden;
n	den Wert 0 oder 1 aufweist;
ALK	ist ein aliphatischer Kohlenwasserstoff mit 1-8 Kohlenstoffatomen,

und deren pharmazeutisch annehmbaren Salze, dadurch gekennzeichnet, dass ein Amid der Formel II :



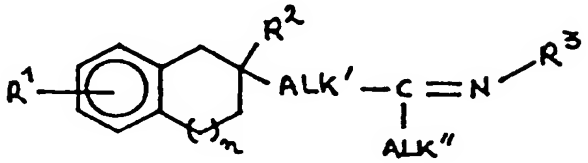
II

ein Nitril der Formel III :



III

oder eine Schiff'sche Base der Formel IV :



IV

reduziert wird, worauf die derart erhaltene Verbindung der Formel I (a) N – alkyliert werden kann, sofert R^3 und/oder R^4 Wasserstoff bedeuten, und/oder (b) in ein pharmazeutisch annehmbares Salz umgewandelt werden kann.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, dass der aromatische Kern unsubstituiert, mono – oder disubstituiert ist, und R^2 $C_1 - C_4$ – Alkyl ist, R^3 und R^4 ausgewählt sind aus H, $C_1 - C_4$ – Alkyl oder zusammen mit dem Stickstoffatom einen Piperazin – oder 4 – Methylpiperazinring bilden und ALK Methylen oder Aethylen ist.

3. Verfahren nach Anspruch 1 oder 2, dadurch gekennzeichnet, dass der aromatische Kern unsubstituiert ist, und R^2 CH_3 ist, R^3 CH_3 oder H ist, R^4 H ist, ALK Methylen ist und n 0 oder 1 ist.

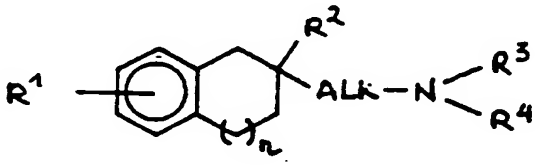
4. Verfahren nach den Ansprüchen 1 – 3, dadurch gekennzeichnet, dass der aromatische Kern unsubstituiert ist, und R^2 und R^3 CH_3 bedeuten, R^4 H ist, ALK Methylen ist und n 0 oder 1 ist.

5. Verfahren nach den Ansprüchen 1 – 3, dadurch gekennzeichnet, dass der aromatische Kern unsubstituiert ist, und R^2 CH_3 ist, R^3 und R^4 H sind, ALK Methylen ist und n null bedeutet.

Revendications

Revendication pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, NL, SE

1. Dérivés de tétrahydronaphtalène et d'indane répondant à la formule générale I :



I

dans laquelle

R^1	représente zéro à quatre substituants qui peuvent être identiques ou différents et sont choisis parmi OH, les halogènes, NO_2, CN, CF_3, les groupe alkyle en C_1-C_4, alcoxy en C_1-C_4 et amino non substitué ou substitué par alkyle en C_1-C_4 ;
R^2	représente un groupe alkyle en C_1-C_4, alcényle en C_1-C_4 ou alcynyle en C_1-C_4 qui peut être substitué par un halogène ;
R_3 et R^4	représentent indépendamment H, un groupe alkyle en C_1-C_4, ou forment avec l'atome d'azote un cycle penta- ou hexagonal ;
n	a la valeur 0 ou 1 ;
ALK	est un hydrocarbure aliphatique de 1 à 8 atomes de carbone ;

et leurs sels pharmaceutiquement acceptables.

2. Composés selon la revendication 1 ayant un noyau aromatique non substitué, mono- ou disubstitué, dans lesquels R^2 est un groupe alkyle en C_1-C_4, R^3 et R^4 sont choisis parmi H, les groupe alkyle en C_1-C_4, ou forment avec l'atome d'azote un cycle de pipérazine ou 4-méthylpipérazine, ALK est un groupe méthylène ou éthylène, et leurs sels pharmaceutiquement acceptables.

3. Composés selon la revendication 1 ou 2, dans lesquels le noyau aromatique n'est pas substitué et R^2 est CH_3, R^3 est CH_3 ou H, R^4 est H, ALK est le groupe méthylène, n est 0 ou 1, et leurs sels pharmaceutiquement acceptables.

4. Composés selon les revendications 1 à 3, dans lesquels le noyau aromatique n'est pas substitué et R^2 et R^3 sont CH_3, R^4 est H, ALK est le groupe méthylène, n est 0 ou 1, et leurs sels pharmaceutiquement acceptables.

5. Composés selon les revendications 1 à 3, dans lesquels le noyau aromatique n'est pas substitué et R^2 est CH_3, R^3 et R^4 sont H, ALK est le groupe méthylène, n est 0, et leurs sels pharmaceutiquement acceptables.

6. Procédé par analogie pour la préparation d'un composé selon la revendication 1, dans lequel un amide de formule II, un nitrile de formule III ou une base de Schiff de formule IV est réduit, après quoi le composé de formule I ainsi obtenu (a) peut être alkylé sur N si R^3 et/ou R^4 sont de l'hydrogène et/ou (b) peut être converti en un sel pharmaceutiquement acceptable.

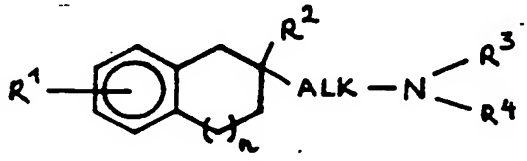
7. Préparation pharmaceutique contenant un composé selon la revendication 1 comme principe actif en mélange avec un support pharmaceutiquement acceptable.

8. Utilisation de composés selon la revendication 1 pour la préparation d'un médicament doué d'activité antidépressive.

9. Les composés de l'une quelconque des revendications 1 à 5 pour leur utilisation en thérapie.

Revendications pour les Etats contractants suivants : ES, GR

1. Un procédé pour la préparation de dérivés de tétrahydronaphtalène et d'indane répondant à la formule générale I :



I

dans laquelle

R^1 représente zéro à quatre substituants qui peuvent être identiques ou différents et sont choisis parmi OH, les halogènes, NO_2, CN, CF_3, les groupe alkyle en $C_1 - C_4$, alcoxy en $C_1 - C_4$ et amino non substitué ou substitué par alkyle en $C_1 - C_4$;

R^2 représente un groupe alkyle en $C_1 - C_4$, alcényle en $C_1 - C_4$ ou alcynyle en $C_1 - C_4$ qui peut être substitué par un halogène ;

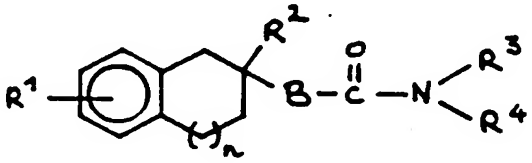
R_3 et R^4 représentent indépendamment H, un groupe alkyle en $C_1 - C_4$, ou forment avec l'atome d'azote un cycle penta - ou hexagonal ;

n a la valeur 0 ou 1 ;

ALK est un hydrocarbure aliphatique de 1 à 8 atomes de carbone ;

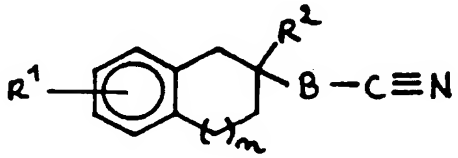
et de leurs sels pharmaceutiquement acceptables,

caractérisé en ce qu'un amide de formule II



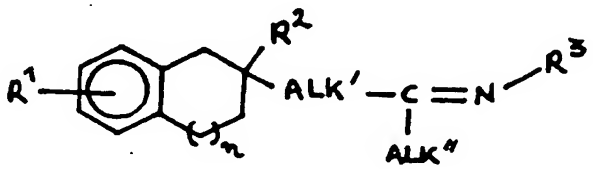
II

un nitrile de formule III



III

ou une base de Schiff de formule IV



IV

est réduit, après quoi le composé de formule I ainsi obtenu (a) peut être alkylé sur N si R^3 et/ou R^4 sont de l'hydrogène et/ou (b) peut être converti en un sel pharmaceutiquement acceptable.

2. Le procédé selon la revendication 1, dans lequel le noyau aromatique est non substitué, mono- ou disubstitué, et R^2 est un groupe alkyle en $C_1 - C_4$, R^3 et R^4 sont choisis parmi H, les groupes alkyle en $C_1 - C_4$, ou forment avec l'atome d'azote un cycle de pipérazine ou 4-méthylpipérazine, et ALK est le groupe méthylène ou éthylène.

3. Le procédé selon la revendication 1 ou 2, dans lequel le noyau aromatique n'est pas substitué et R^2 est CH_3, R^3 est CH_3 ou H, R^4 est H, ALK est le groupe méthylène et n est 0 ou 1.

4. Le procédé selon les revendications 1 à 3, dans lequel le noyau aromatique n'est pas substitué et R^2 et R^3 sont CH_3, R^4 est H, ALK est le groupe méthylène et n est 0 ou 1.

5. Le procédé selon les revendications 1 à 3, dans lequel le noyau aromatique n'est pas substitué et R^2 est CH_3, R^3 et R^4 sont H, ALK est le groupe méthylène et n est 0.